Risk adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first line therapy

Petrausch, U ; Samaras, P ; Haile, S R ; Veit-Haibach, P ; Soyka, J D ; Knuth, A ; Hany, T F ; Mischo, A ; Renner, C ; Schäefer, N G

Abstract: BACKGROUND: The purpose of this study was to evaluate the impact of 2-[fluorine-18]fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) during follow-up of patients with diffuse large B-cell lymphoma (DLBCL) being in complete remission or unconfirmed complete remission after first-line therapy. PATIENTS AND METHODS: DLBCL patients receiving FDG-PET/CT during follow-up were analyzed retrospectively. Confirmatory biopsy was mandatory in cases of suspected disease recurrence. RESULTS: Seventy-five patients were analyzed and 23 (30%) had disease recurrence. The positive predictive value (PPV) of FDG-PET/CT was 0.85. Patients >60 years [P = 0.036, hazard ratio (HR) = 3.82, 95% confidence interval (CI) 1.02-7.77] and patients with symptoms indicative of a relapse (P = 0.015; HR = 4.1; 95% CI 1.20-14.03) had a significantly higher risk for relapse. A risk score on the basis of signs of relapse, age >60 years, or a combination of these factors identified patients at high risk for recurrence (P = 0.041). CONCLUSIONS: FDG-PET/CT detects recurrent DLBCL after first-line therapy with high PPV. However, it should not be used routinely and if only in selected high-risk patients to reduce radiation burden and costs. On the basis of our retrospective data, FDG-PET/CT during follow-up is indicated for patients <60 years with clinical signs of relapse and in patients >60 years with and without clinical signs of relapse.

DOI: https://doi.org/10.1093/annonc/mdq015

original article

Annals of Oncology 21: 1694–1698, 2010
doi:10.1093/annonc/mdq015
Published online 5 February 2010

Risk-adapted FDG–PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy

U. Petrausch[1†], P. Samaras[1†], S. R. Haile[2], P. Veit-Haibach[3], J. D. Soyka[3], A. Knuth[1], T. F. Hany[3], A. Mischo[1], C. Renner[1†] & N. G. Schäefer[1,3*†]

[1]*Department of Oncology, University Hospital Zurich;* [2]*Biostatistics Unit, Institute of Social and Preventive Medicine, University of Zurich and* [3]*Division of Nuclear Medicine, Department of Medical Radiology, University Hospital Zurich, Zürich, Switzerland*

Received 10 December 2009; revised 18 December 2009; accepted 21 December 2009

Background: The purpose of this study was to evaluate the impact of 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography/computed tomography (FDG–PET/CT) during follow-up of patients with diffuse large B-cell lymphoma (DLBCL) being in complete remission or unconfirmed complete remission after first-line therapy.
Patients and methods: DLBCL patients receiving FDG–PET/CT during follow-up were analyzed retrospectively. Confirmatory biopsy was mandatory in cases of suspected disease recurrence.
Results: Seventy-five patients were analyzed and 23 (30%) had disease recurrence. The positive predictive value (PPV) of FDG–PET/CT was 0.85. Patients >60 years [$P = 0.036$, hazard ratio (HR) = 3.82, 95% confidence interval (CI) 1.02–7.77] and patients with symptoms indicative of a relapse ($P = 0.015$; HR = 4.1; 95% CI 1.20–14.03) had a significantly higher risk for relapse. A risk score on the basis of signs of relapse, age >60 years, or a combination of these factors identified patients at high risk for recurrence ($P = 0.041$).
Conclusions: FDG–PET/CT detects recurrent DLBCL after first-line therapy with high PPV. However, it should not be used routinely and if only in selected high-risk patients to reduce radiation burden and costs. On the basis of our retrospective data, FDG–PET/CT during follow-up is indicated for patients <60 years with clinical signs of relapse and in patients >60 years with and without clinical signs of relapse.
Key words: diffuse large B-cell lymphoma, FDG–PET/CT, follow-up, positive predictive value

introduction

The prognosis for patients with diffuse large B-cell lymphoma (DLBCL) has improved after implementation of rituximab in first-line chemotherapy, and a chance of cure also exists after salvage therapy in case of relapse [1–3]. However, the improvement seen from the use of rituximab in first-line treatment may negatively impact on the chance of cure when patients present with relapsed disease [4]. Therefore, efforts have to be undertaken to develop optimized follow-up procedures that detect relapse at an early or even preclinical stage on the basis of the assumption that early detection of relapse may allow onset of re-treatment at an early time point and, eventually, improve survival. Current DLBCL guidelines recommend radiological examinations at 6, 12 and 24 months after end of treatment by computed tomography (CT) [5]. The use of 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography (FDG–PET) has been established for the initial staging and the assessment of treatment response during and after completion of first-line therapy in lymphoma patients [6], but only limited data are available regarding the impact of FDG–PET for the follow-up of DLBCL patients who achieved a complete remission (CR) or complete remission unconfirmed (CRu) after initial therapy [7]. As of today, only two prospective studies evaluating FDG–PET during follow-up of lymphoma patients have been reported, with one study focusing exclusively on patients with Hodgkin's lymphoma (HL) [8]. In the other study with a cohort of 183 patients with aggressive non-Hodgkin's lymphoma, the use of FDG–PET led to earlier diagnosis of relapse compared with CT, and the authors concluded that FDG–PET may be a valid tool for the routine follow-up of lymphoma patients [9]. However, this conclusion is debatable from our point of view because of rising concerns over the increasing use of imaging modalities with regard to patient safety and health care costs. We recently identified the risk factors residual mass, advanced stage and symptoms in HL patients, indicating a high-risk situation for relapse, which may justify the use of FDG–PET for follow-up [10]. In the present study, we identify DLBCL patients at high

Correspondence to: Dr N. G. Schäfer, Department of Oncology, University Hospital Zurich, Rämistrasse 100, 8091 Zürich, Switzerland. Tel: +41-44-255-1111; Fax: +41-44-255-4548; E-mail: niklaus.schaefer@usz.ch

†These authors contributed equally to this work.

risk for relapse by retrospective analysis of our patient database. The aim of this analysis was the development of a risk-adapted strategy for the follow-up of DLBCL patients that may help to reduce the radiation exposure of our patients and health care costs.

patients and methods

patients

Patients with DLBCL in CR or CRu after first-line treatment who received at least one FDG–PET combined with CT during their follow-up from the beginning of 2002 until the end of 2008 were included in this study. FDG–PET imaging data were acquired on a combined FDG–PET in-line system (Discovery LS, RX or Discovery STE; GE Health Systems, Milwaukee, WI), which permits the acquisition of co-registered CT and FDG–PET (FDG–PET/CT) images in a single session.

All FDG–PET/CT scans were evaluated for the presence of abnormal FDG uptake and residual disease. All image analysis was routinely carried out by two dual board-certified nuclear radiology physicians in consensus. CR in these patients had to be documented by one appropriate imaging modality within 1 month after completion of first-line treatment (CT alone, CT and FDG–PET, or FDG–PET/CT). All imaging was carried out at our institution. CT scans were assessed for residual disease using the International Workshop Criteria (IWC) [11].

A residual morphological mass after the end of treatment was defined as a lesion that had regressed by >75% but was still >1.5 cm in its greatest axial diameter (CRu). We further documented the initial stage of disease using the Ann Arbor classification. Age, gender and signs of recurrence were assessed and recorded by the referring physician before the follow-up FDG–PET imaging was carried out. Signs of recurrence included B symptoms or new suspicious masses. Relapse-free survival (RFS) was assessed in all patients from the initial date of diagnosis until the date of recurrence as documented by FDG–PET/CT. Histological confirmation was mandatory in all patients with suspected recurrent disease. Our institutional ethics committee had approved the study. Due to the retrospective nature of the study, written informed consent of the patients was waived.

assessment of risk factors and patient classification

CT scans after the completion of first-line treatment were assessed for residual morphological masses at the initial lymphoma sites using the IWC as described above. Patients were assessed for advanced (IIIA–IVB) versus early (IA–IIB) initial stage by Ann Arbor classification, extranodal disease present versus absent, age and gender. Patient classification into the symptomatic or asymptomatic group was done on the basis of reported symptoms or referral notes by the treating physician.

statistical analysis

The primary goal was to provide estimates of survival for different values of the variables provided. Kaplan–Meier plots are a graphical method to represent the survival curves for each subgroup, using stratification. Additionally, Cox proportional hazards regression was used to determine whether the effect of the various factors (residual mass, extranodal disease, initial stage, and presence of symptoms) was statistically significant, through the use of a log-rank test. All analysis was carried out in the R programming language, using the survival package [12].

results

patients and disease status

We collected data from patients with DLBCL who received one or more follow-up FDG–PET/CT scans from 2002 to 2008 at our institution. From 138 patients initially indexed, 63 patients had to be excluded from analysis due to incomplete follow-up data or administration of salvage therapy before FDG–PET/CT was carried out. Overall, 75 patients with confirmed DLBCL (45 male, 30 female; mean age 60; range from 23 to 90 years) had sufficient follow-up data and were eligible for analysis. The median follow-up was 16.5 months (range 6–93 months) for the entire patient cohort. Patient characteristics are depicted in Table 1. The patients had initially received CT alone ($n = 19$), FDG–PET ($n = 8$), or FDG–PET/CT ($n = 48$) after completion of first-line therapy. The median RFS was 57 months in the entire patient cohort (range 7.7–93 months; Figure 1A).

Of the total number of 75 patients studied, twenty-seven (36%) had a positive FDG–PET/CT during follow-up. Of all 75 patients, 40 (53%) received FDG–PET/CT due to clinical signs indicating a relapse. From these 40 symptomatic patients, 23 (52.5%) had a positive FDG–PET and in 20 (50%), relapse

Table 1. Asymptomatic and symptomatic patient groups

	n	%
Asymptomatic patients ($n = 35$)		
FDG–PET/CT		
Positive	4	11.5
Negative	31	88.5
Recurrence		
Yes	3	8.6
No	32	91.4
Morphological residual mass		
Yes	14	40.0
No	21	60.0
Stage of disease		
Early (IA–IIB)	23	65.7
Advanced (IIIA–IVB)	12	34.3
Extranodal disease		
Yes	17	50.0
No	17	50.0
Advanced age (years)		
<60	20	57.2
>60	15	42.8
Symptomatic patients ($n = 40$)		
FDG–PET/CT		
Positive	23	57.5
Negative	17	42.5
Recurrence		
Yes	20	50.0
No	20	50.0
Morphological residual mass		
Yes	32	80.0
No	8	20.0
Stage of disease		
Early (IA–IIB)	17	42.5
Advanced (IIIA–IVB)	23	57.5
Extranodal disease		
Yes	20	50.0
No	20	50.0
Advanced age (years)		
<60	14	35.0
>60	26	65.0

FDG–PET/CT, 2-[fluorine-18]fluoro-2-deoxy-D-glucose–positron emission tomography/computed tomography.

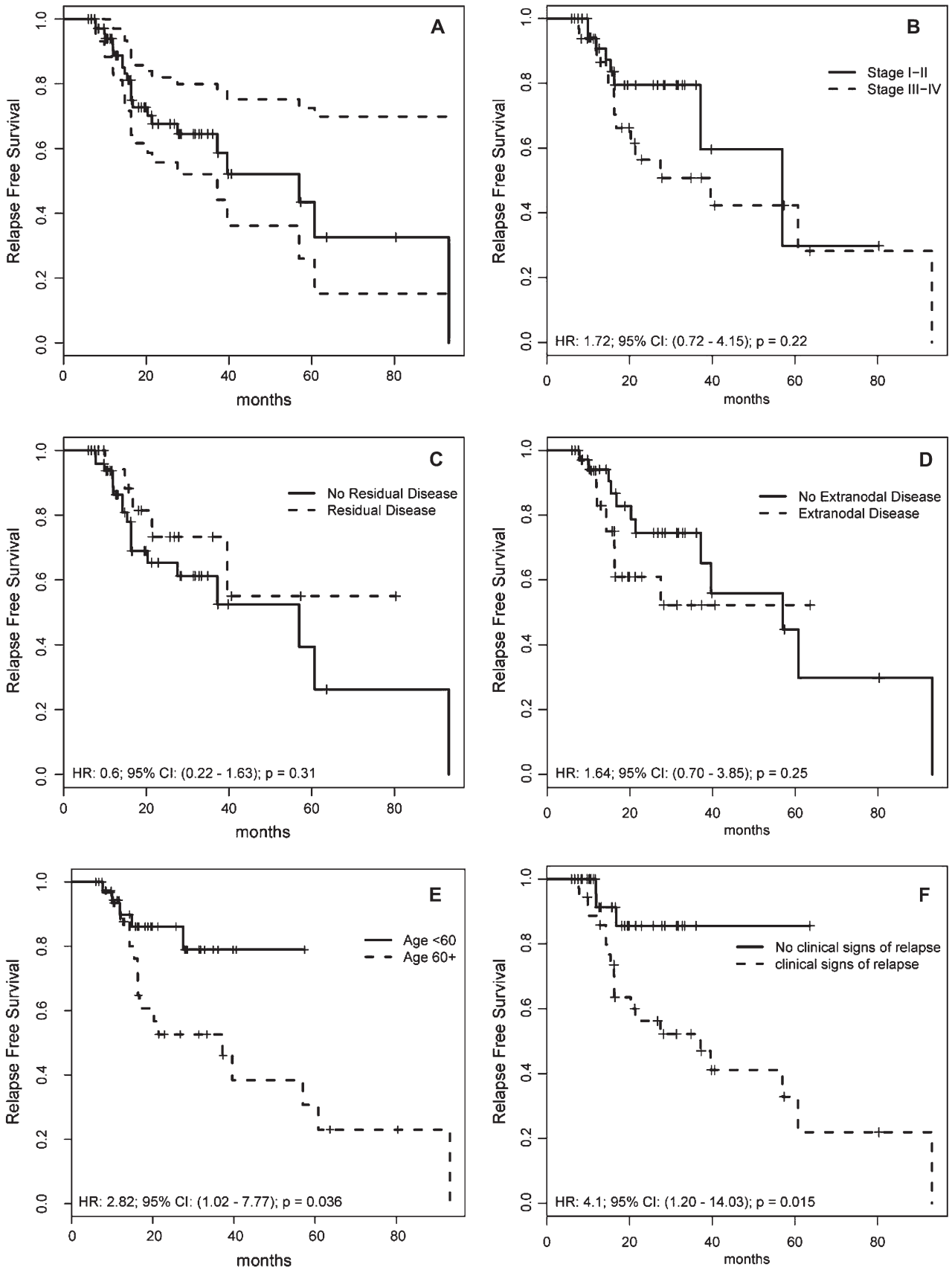

Figure 1. Kaplan–Meier analysis of all patients [dashed line: 95% confidence interval (CI) (A)]. Univariate analysis for Ann Arbor classification (B), residual disease after first-line therapy (C), extranodal disease (D), age (E) and clinical signs of relapse (F).

was confirmed by biopsy. One patient had positive PET due to secondary carcinoma of the lung and in two patients, the biopsy showed no malignant cells. In the remaining group of 35 asymptomatic patients, 4 patients had a positive PET, and in 3 of them, relapse was confirmed by biopsy. A biopsy of one patient showed no malignant cells. Overall, for all 75 patients, FDG–PET/CT was able to detect relapses with a positive predictive value (PPV) of 0.85.

In 21 patients (91%) from 23 relapsed patients sufficient follow-up could be performed. The median RFS until the second relapse was 16 months (range 1.4–99 months). In relapsed patients, there was no significant difference in the RFS until the second relapse for patients >60 years [$n = 17$ patients, $P = 0.83$; hazard ratio (HR) = 0.88; 95% confidence interval (CI) 0.20–3.61] compared with younger patients ($n = 4$) and with clinical signs of relapse at time of the first relapse ($n = 18$ patients, $P = 0.74$; HR = 1.39; 95% CI 0.13–17.51) compared with no clinical signs ($n = 3$).

risk factor assessment

We analyzed the initial stage at diagnosis by Ann Arbor classification, residual disease after first-line therapy, extranodal disease, age and clinical signs of relapse by univariate analysis. Stage at diagnosis ($P = 0.22$; HR = 1.72; 95% CI 0.72–4.15), residual disease ($P = 0.31$; HR = 0.6; 95% CI 0.22–1.63), and extranodal disease ($P = 0.25$; HR = 1.64; 95% CI 0.70–3.85) were not statistically significant predictors for relapse. Patients >60 years ($P = 0.036$; HR = 2.82; 95% CI 1.02–7.77) and patients with symptoms indicative of relapse ($P = 0.015$; HR = 4.1; 95% CI 1.20–14.03) had a significantly shorter RFS (Figure 1B–E).

A risk score including age >60 years and clinical signs of relapse (zero to two risk factors) identified patients at high risk for recurrence ($P = 0.041$). Only 1 patient from 20 patients without symptoms and age <60 years had positive FDG–PET/CT scans and a biopsy-proven relapse (Table 2). The median RFS was not reached in patients without any of these risk factors (Figure 2).

Table 2. Positive PET/CT and proven relapse by biopsy for all patients and patients separated by age

	Signs of clinical relapse	No signs of clinical relapse
All patients, $n = 75$	n (%), $n = 40$	n (%), $n = 35$
PET/CT positive	23 (57.5)	4 (11.5)
Biopsy positive	20 (50.0)	3 (8.6)
<60 years, $n = 34$	$n = 14$	$n = 20$
PET/CT positive	4 (28.6)	1 (5.0)
Biopsy positive	4 (28.6)	1 (5.0)
>60 years, $n = 41$	$n = 26$	$n = 15$
PET/CT positive	19 (73.1)	3 (20.0)
Biopsy positive	16 (61.5)	2 (13.3)

PET/CT, positron emission tomography–computed tomography.

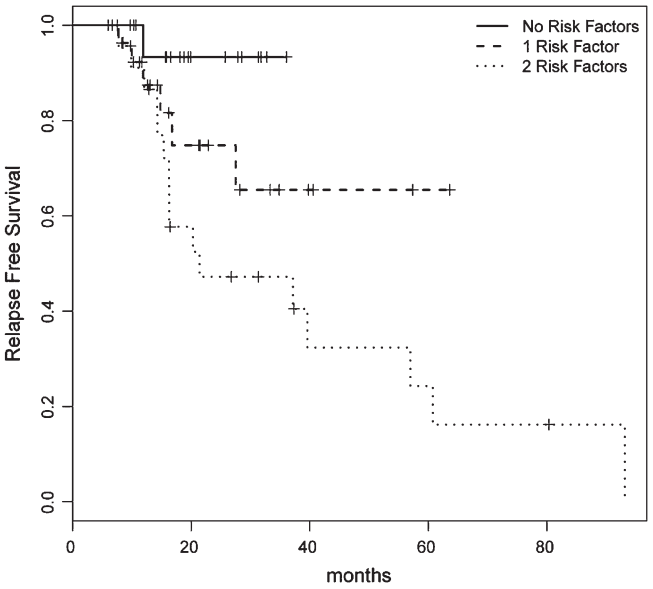

Figure 2. Kaplan–Meier analysis of the relapse-free survival of patients with the risk factors clinical signs of relapse and age >60 years (solid line: zero risk factors, dashed line: one risk factor, pointed line: two risk factors), $P < 0.05$.

discussion

In the present study, we evaluated the impact of FDG–PET/CT during the follow-up of patients with DLBCL who achieved a CR or CRu after first-line treatment. Seventy-five patients with CR or CRu after completion of first-line therapy were eligible for the analysis. We evaluated symptomatic as well as asymptomatic patients with regard to the risk factors advanced stage of disease, residual disease after completion of therapy, extranodal disease, patient age and clinical signs of relapse. We intended to identify retrospectively risk factors for relapse that may help to individualize the use of FDG–PET/CT during follow-up and to reduce irradiation burden and treatment costs. Symptoms as the reason for patient referral and patient age >60 years were the most important risk factors. Both factors were used in a risk score. The score was created with the objective of assessing the risk of relapse for a patient and the benefit of further imaging. Age >60 years or clinical symptoms alone or the combination indicated high risk of relapse and, therefore, justified intensified imaging. The PPV of 0.85 is in accordance with other studies but also demonstrated again that relapse has to be proven by biopsy [13]—may be especially when rituximab-containing regimens were used [14].

Our results have to be interpreted in the context of the current guidelines for the follow-up of DLBCL and the most recently published prospective study of FDG–PET-based surveillance by Zinzani et al. [5, 9]. In our study, patients <60 years with no clinical signs of relapse and no extranodal disease have very low risk of relapse. Therefore, these patients may not benefit from FDG–PET/CT scans during follow-up. According to our analysis, the only indication for FDG–PET in younger patients are clinical signs of relapse.

However, to finally implement these risk factors and their consequences in regard to imaging-based surveillance, treatment and survival for high- and low-risk patients, a prospective trial has to be carried out. In this trial, patients

would need to be stratified for the risk factors described here and then, PET/CT has to be tested versus CT alone at 6, 12 and 24 months after end of first-line treatment.

The study of Zinzani et al. indicates the use of FDG–PET/CT for all patients with aggressive lymphoma. In contrast, on the basis of the identification of this low-risk patient group, ∼25% of the patients could be spared FDG–PET/CT scans. The RFS decreased markedly in patients with a higher risk score. Patients >60 years with clinical signs of relapse are at high risk for relapse. In this situation, routine FDG–PET/CT appears to be justified during follow-up. Nevertheless, the impact on better survival due to earlier detection of disease recurrence has yet to be proven in prospective randomized studies. Therefore, at the moment, there is no indication in the routine follow-up of patients with PET/CT. This relatively new technique, if used, should be limited to selected patients that are at high risk for recurrence [15].

The retrospective nature of this study and the relatively small patient number are the most important limitations. Additionally, FDG–PET/CT was not mandatory after first-line treatment for the inclusion into the analysis because the revised response criteria for malignant lymphoma were published in 2007 and our analysis included patients from 2002 to 2008. FDG–PET/CT surveillance was not done at fix time points after the end of the first-line treatment. The goal of our retrospective analysis was rather to develop a rationale for the use of FDG–PET/CT imaging in a well-defined patient population with DLBCL after the completion of the first-line therapy.

In conclusion, FDG–PET/CT reliably detects recurrent DLBCL after first-line therapy. FDG–PET/CT can be considered during follow-up in high-risk patients for relapse with age <60 years when clinical signs of relapse are present and in patients with age >60 years regardless of clinical symptoms of relapse. However, the routine use of PET/CT during follow-up cannot be recommended until prospective trials have demonstrated a survival benefit for patients followed by PET/CT.

acknowledgements

UP: writing manuscript, data analysis; PS: writing manuscript, data analysis; SRH: statistical data analysis; PV-H: image analysis; JDS: image analysis; AM: data analysis; AK: scientific support (oncology); TFH: scientific support (nuclear medicine); CR: integrity of study, writing manuscript; NGS: study design, data analysis, writing manuscript.

references

1. Hernandez-Ilizaliturri FJ, Czuczman MS. Therapeutic options in relapsed or refractory diffuse large B-cell lymphoma. Part 2. Novel therapeutic strategies. Oncology (Williston Park) 2009; 23: 610–615.
2. Hernandez-Ilizaliturri FJ, Czuczman MS. Therapeutic options in relapsed or refractory diffuse large B-cell lymphoma. Part 1. current treatment approaches. Oncology (Williston Park) 2009; 23: 546–553.
3. Held G, Schubert J, Reiser M, Pfreundschuh M. Dose-intensified treatment of advanced-stage diffuse large B-cell lymphomas. Semin Hematol 2006; 43: 221–229.
4. Hagberg H, Gisselbrecht C. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. Ann Oncol 2006; 17 (Suppl 4): iv31–iv32.
5. Tilly H, Dreyling M. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009; 20 (Suppl 4): 110–112.
6. Hutchings M, Barrington SF. PET/CT for therapy response assessment in lymphoma. J Nucl Med 2009; 50 (Suppl 1): 21S–30S.
7. Lister TA, Crowther D, Sutcliffe SB et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989; 7: 1630–1636.
8. Jerusalem G, Beguin Y, Fassotte MF et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. Ann Oncol 2003; 14: 123–130.
9. Zinzani PL, Stefoni V, Tani M et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. J Clin Oncol 2009; 27: 1781–1787.
10. Petrausch U, Samaras P, Veit-Haibach P et al. Hodgkin's lymphoma in remission after first-line therapy: which patients need FDG-PET/CT for follow-up? Ann Oncol 2010; 21(5): 1053-1057.
11. Juweid ME, Stroobants S, Hoekstra OS et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007; 25: 571–578.
12. Development Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. 2005.
13. Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood 2007; 110: 3507–3516.
14. Han HS, Escalon MP, Hsiao B et al. High incidence of false-positive PET scans in patients with aggressive non-Hodgkin's lymphoma treated with rituximab-containing regimens. Ann Oncol 2009; 20: 309–318.
15. Cheson B. The case against heavy PETing. J Clin Oncol 2009; 27: 1742–1743.